

U.S.S.N.: 09/345,712

Filed: June 30, 1999

## AMENDMENT AND RESPONSE TO OFFICE ACTION

cf 19. The method of claim 10 wherein the disorder is recessive dystrophic epidermolysis bullosa.

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**Remarks**

Allowance of claims 10-12 and 18 is greatly appreciated.

Rejection under 35 U.S.C. 112

Claim 6 was rejected under 35 U.S.C. 112 as indefinite. This rejection is respectfully traversed if applied to the amended claim. The claim language has been inserted into claim 4, amended to delete "like TNP-470" and to insert the word "anti-angiogenic" as the modifier for the fumagillin compounds. Claim 6 is now specific for TNP-470.

Rejection under 35 U.S.C. 103

Claims 4, 5, 6, and 17 were rejected under 35 U.S.C. 103 as obvious over WO 99/29878 to Sukhatme, Doland's Medical Dictionary 1994, U.S. Patent No. 5,696,147 to Galardy, and U.S. Patent No. 5,733,876 to O'Reilly, et al. These rejections are respectfully traversed if applied to the amended claims.

*Sukhatme and O'Reilly*

Claims 4 and 17 have been amended to delete endostatin and angiostatin type inhibitors. This should overcome the rejections based on the disclosure in Sukhatme and O'Reilly, et al. since these are restricted to endostatin and angiostatin.

*Galardy*

Claims 4 and 5 of the use of topical metalloproteinase inhibitors for epidermolysis bullosa were rejected on the basis of Galardy. Galardy discloses the use of metalloproteinase

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inhibitors which are hydroxamate derivatives. The hydroxamate derivatives described by Galardy are direct inhibitors of metalloproteinases which act through a distinct mechanism, that is chelation of zinc ion, and are therefore not inhibitors of angiogenesis. The claimed matrix metalloproteinases such as curcumin and curcuminoids do not directly antagonize the activity of the matrix metalloproteinases themselves, but inhibit the synthesis of matrix metalloproteinases by transcriptional and translational mechanisms. The synthesis of these enzymes is strictly regulated, and curcumin acts by inhibiting the production of metalloproteinases and/or stimulating the synthesis of proteins that directly inhibit the activity of metalloproteinases, such as tissue inhibitor of matrix metalloproteinases. To determine that direct inhibition of metalloproteinase activity covers inhibition of synthesis of metalloproteinases is akin to disallowing a patent for penicillin because sulfanilamide also kills bacteria.

However, to facilitate prosecution, "epidermolysis bullosa" has been deleted from claim 4, and added as a new claim 19 dependent on allowed claim 10.

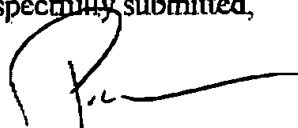
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Allowance of Claims 4, 5, 6, 10-12, 17, 18 and 19, is earnestly solicited.

Respectfully submitted,



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## Appendix: Marked Up Copy of Amended Claims

4. (three times amended) A method for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, ~~neurofibromatosis~~ <sup>neurofibromas</sup>, tuberous sclerosis, [recessive dystrophic epidermolysis bullosa,] venous ulcers, molluscum contagiosum, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor wherein the angiogenesis inhibitor is selected from the group consisting of collagenase inhibitors, angiogenic fumagillin derivatives, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12 in an amount effective to inhibit angiogenesis.

5. The method of claim 4 wherein the angiogenesis inhibitor is applied topically.

6. (amended) The method of claim 5 wherein the angiogenesis inhibitor is [selected from the group consisting of collagenase inhibitors, endostatin, angiostatin, fumagillin derivatives like] TNP-470[, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12].

10. (twice amended) A method to treat the symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, malignant melanoma and Kaposi's sarcoma, comprising administering to the individual in need of treatment an effective amount of a curcuminoid to inhibit angiogenesis.

11. (amended) The method of claim 10 wherein the curcuminoid is curcumin.

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12. (amended) The method of claim 10 wherein the curcuminoid is demethoxycurcumin.

17. (twice amended) A method for inhibiting skin disorders selected from the group consisting of lymphangiogenesis, hemangioma of childhood, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, pyogenic granulomas, recessive dystrophic epidermolysis bullosa, venous ulcers, rosacea, eczema, molluscum contagiosum, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis, wherein the angiogenesis inhibitor is selected from the group consisting of

tetracyclines inhibiting collagenase,

[endostatin,] and

a sulfated polysaccharide which inhibits angiogenesis.

18. The method of claim 10 wherein the disorder is malignant melanoma.

Please add new claim 19.

19. The method of claim 10 wherein the disorder is recessive dystrophic epidermolysis bullosa.

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## APPENDIX: Clean Copy of Claims as Amended

4. (three times amended) A method for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor wherein the angiogenesis inhibitor is selected from the group consisting of collagenase inhibitors, angiogenic fumagillin derivatives, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12 in an amount effective to inhibit angiogenesis.

5. The method of claim 4 wherein the angiogenesis inhibitor is applied topically.

6. (amended) The method of claim 5 wherein the angiogenesis inhibitor is TNP-470.

10. (twice amended) A method to treat the symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, malignant melanoma and Kaposi's sarcoma, comprising administering to the individual in need of treatment an effective amount of a curcuminoid to inhibit angiogenesis.

11. (amended) The method of claim 10 wherein the curcuminoid is curcumin.

12. (amended) The method of claim 10 wherein the curcuminoid is demethoxycurcumin.

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17. (twice amended) A method for inhibiting skin disorders selected from the group consisting of lymphangiogenesis, hemangioma of childhood, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, pyogenic granulomas, recessive dystrophic epidermolysis bullosa, venous ulcers, rosacea, eczema, molluscum contagiosum, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis, wherein the angiogenesis inhibitor is selected from the group consisting of

tetracyclines inhibiting collagenase, and

a sulfated polysaccharide which inhibits angiogenesis.

18. The method of claim 10 wherein the disorder is malignant melanoma.

19. The method of claim 10 wherein the disorder is recessive dystrophic epidermolysis bullosa.

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